

Mesenchymal Stem Cell-Derived Paracrine Products as Senotherapeutic Interventions for Skin Photoaging: A Preclinical Systematic Review of the Senescence-SASP Axis

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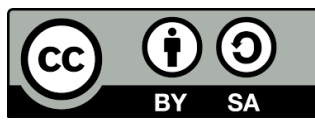
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Skin Photoaging; Cellular Senescence; SASP; Mesenchymal Stem Cell Secretome; Extracellular Vesicles Senotherapeutics.

ABSTRACT

Chronic ultraviolet (UV) exposure induces oxidative stress, mitochondrial dysfunction, DNA damage, and cell cycle arrest through the p53/p21^{CIP1} and p16^{INK4a} pathways, contributing to cellular senescence and the development of the senescence-associated secretory phenotype (SASP). Objective: This study aimed to synthesize evidence on how mesenchymal stem cell (MSC)-derived secretomes, conditioned media, and extracellular vesicles (EVs) modulate the senescence-SASP axis in UV-induced skin photoaging and to evaluate their translational potential. Methods: Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines, PubMed, Scopus, and Web of Science were searched for original studies published between January 2021 and July 2026 using terms related to skin photoaging, MSC-derived secretomes, conditioned media, EVs/exosomes, cellular senescence, SASP, and senotherapeutics. Eligible studies investigated MSC-derived secretomes, conditioned media, or EVs in UV- or oxidative stress-induced skin models and reported senescence biomarkers, SASP mediators, or associated molecular pathways. Of the 211 records identified, 149 remained after duplicate removal, and 15 underwent full-text assessment, resulting in eight studies included in the qualitative synthesis. All eight studies were preclinical and employed in vitro and/or in vivo UVA/UVB exposure models. MSC sources included umbilical cord tissue, adipose tissue, and hair follicles. Two studies investigated adipose-derived MSCs subjected to hypoxic or three-dimensional culture preconditioning, while two examined engineered molecular cargo (miR-125b-5p and circ_0011129). Results: MSC-derived secretome and EV treatments consistently reduced senescence markers, oxidative stress, and DNA damage while preserving collagen and elastin. The implicated mechanisms included PINK1/Parkin-mediated mitophagy, GATA2/PZP/GRP75 signaling, the TIMP1-ADAM10-Notch1-HES1 axis, and TGF- β 1/Smad signaling. However, canonical SASP mediators were evaluated in only four studies. Delivery methods also influenced treatment efficacy, with subcutaneous injection and microneedle-assisted administration demonstrating effects on dermal tissue.



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INTRODUCTION

Skin photoaging is a complex biological process primarily caused by chronic ultraviolet (UV) radiation exposure and clinically characterized by wrinkles, loss of skin elasticity, dyspigmentation, and impaired skin integrity. Oxidative stress, inflammation, and extracellular matrix (ECM) degradation have long been recognized as key hallmarks of photoaging. However, growing evidence suggests that these processes converge on a common biological mechanism: cellular senescence. Chronic UV exposure induces excessive production of reactive oxygen species (ROS), resulting in oxidative DNA damage, mitochondrial dysfunction, and persistent activation of the DNA damage response (DDR). These events trigger sustained cell-cycle arrest through the p53/p21^{CIP1} and p16^{INK4a} pathways, leading to the accumulation of senescent dermal fibroblasts and keratinocytes (Lohakul et al., 2022; Guo et al., 2022; Miwa et al., 2022).

Rather than remaining biologically inactive, senescent cells develop a senescence-associated secretory phenotype (SASP), characterized by the sustained secretion of proinflammatory cytokines, chemokines, growth factors, and matrix metalloproteinases (MMPs). The SASP contributes to a chronic inflammatory microenvironment that exacerbates oxidative stress, promotes secondary senescence in neighboring cells, and accelerates ECM degradation, establishing a self-perpetuating feedback loop that drives progressive skin photoaging (Chin et al., 2023; Konstantinou et al., 2024; Nan et al., 2025). Consequently, the senescence–SASP axis has emerged as a promising therapeutic target, as disrupting this pathological cascade may simultaneously attenuate multiple downstream mechanisms of photoaging rather than addressing individual manifestations separately.

Recent advances in regenerative medicine have shifted therapeutic strategies from conventional cell-based transplantation toward cell-free approaches, particularly those involving mesenchymal stem cell (MSC)-derived paracrine products. These products comprise a heterogeneous array of bioactive mediators secreted by MSCs, including soluble factors present in conditioned medium (CM) and extracellular vesicles (EVs), such as exosomes, which contribute to the paracrine effects traditionally attributed to transplanted MSCs. MSC-derived paracrine products can deliver bioactive proteins, lipids, nucleic acids, and other signaling molecules without administering viable cells. Consequently, these approaches may offer potential advantages over whole-cell therapies by reducing concerns related to cell survival, immunological compatibility, uncontrolled differentiation, and tumorigenicity, although their safety profiles require further investigation (Kumar et al., 2024). Emerging evidence further indicates that the biological effects of MSC-derived products extend beyond tissue repair and regeneration to the modulation of fundamental molecular pathways associated with cellular aging.

The novelty of this systematic review lies in its mechanistically structured synthesis of evidence concerning MSC-derived paracrine products according to the specific levels of the senescence–SASP axis targeted by these interventions: upstream oxidative stress and mitochondrial homeostasis, cell-cycle arrest, SASP-mediated secretory activity, and downstream ECM remodeling and phenotypic outcomes. Unlike previous reviews that have broadly examined MSC-derived secretomes in skin regeneration and aging, this review specifically evaluates the mechanistic evidence linking MSC-derived products to the senescence–SASP axis, identifies systematic gaps in the assessment of relevant biological

endpoints, and critically examines whether the reported effects can be classified as senomorphic, senopreventive, or senolytic. Furthermore, this review highlights the gap between preclinical mechanistic findings and clinical outcomes, providing a framework for future investigations that align molecular and cellular endpoints with the requirements for clinical translation.

Accordingly, this systematic review aims to synthesize and critically evaluate existing evidence regarding the mechanisms through which MSC-derived paracrine products, including conditioned media, EVs, and exosomes, modulate the senescence–SASP axis in UV-induced skin photoaging. Particular emphasis is placed on their effects on cellular senescence, SASP-associated signaling, oxidative stress, mitochondrial dysfunction, inflammatory pathways, and ECM remodeling. The review also assesses the translational potential of these cell-free interventions as emerging senotherapeutic strategies for skin photoaging. By providing a comprehensive, mechanistically organized synthesis, this review seeks to identify critical gaps in the existing evidence, recommend standardized biological endpoints for future investigations, and highlight considerations related to delivery methods, therapeutic efficacy, and safety assessment. These findings are expected to inform the development of more rigorous preclinical studies and support the potential translation of MSC-derived senotherapeutic interventions into clinical applications.

METHOD

Identification of relevant literature

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines (Page et al., 2021). A systematic literature search was performed in PubMed, Scopus, and Web of Science to identify eligible studies published between January 2021 and July 2026. The search was conducted on July 30, 2026, using database-specific Boolean operators and truncation to combine three key concepts: skin photoaging and ultraviolet (UV) exposure; mesenchymal stem cells (MSCs); and secretomes, conditioned media, or extracellular vesicles (EVs), including exosomes. To maximize search sensitivity, criteria related to cellular senescence and the senescence-associated secretory phenotype (SASP) were applied during title, abstract, and full-text screening rather than incorporated into the search strings.

The review included original preclinical and clinical studies that met the predefined eligibility criteria. Titles, abstracts, and full-text articles were independently screened by reviewers. Disagreements regarding study eligibility were resolved through discussion until consensus was reached.

Eligibility Criteria

Inclusion criteria were original research articles published in English between January 2021 and July 2026. We included studies that evaluated mesenchymal stem cell (MSC)-derived secretome, conditioned medium (CM), extracellular vesicles (EVs), or exosomes from any MSC source in models of UV- or oxidative stress-induced skin photoaging, including in vitro, ex vivo, animal, or clinical studies. Eligible studies were required to assess cellular senescence, canonical senescence-associated secretory phenotype (SASP), or mechanistic pathways directly involved in senescence regulation in skin photoaging. Senescence-related outcomes included established senescence biomarkers (e.g., SA- β -gal,

p16^{INK4a}, p21, and p53), canonical SASP mediators, or signaling pathways mechanistically linked to senescence.

For the purposes of this review, canonical SASP was operationally defined as secreted pro-inflammatory cytokines and chemokines quantified at the protein or transcript level, including, where reported, IL-6, IL-8, IL-1 β , and TNF- α . Matrix metalloproteinases (MMPs) were classified separately as the matrix-degrading arm of the photoaging response and were not counted as canonical SASP outcomes, although their regulation was considered in relation to extracellular matrix remodeling and senescence-associated tissue damage. Relevant senescence-associated signaling pathways included NF- κ B, TGF- β /Smad, SIRT1, Nrf2, PINK1/Parkin, and TIMP1/Notch1. Studies reporting SASP mediators without senescence markers were eligible under the SASP arm.

Studies were excluded if they were reviews, editorials, conference abstracts, preprints, letters, case reports, or duplicates. Studies assessing whole-cell MSC transplantation without a secretome or EV component, non-MSC-derived conditioned media or extracellular vesicles, or non-cutaneous models were also excluded. Additionally, studies focused solely on cosmetic or regenerative outcomes, such as wrinkle reduction, collagen synthesis, antioxidant effects, or delivery technologies, without assessment of cellular senescence, canonical SASP, or mechanistically relevant senescence pathways were excluded. Studies that were not available as full text after reasonable attempts to retrieve the article were excluded from the qualitative synthesis.

Assessment of Risk of Bias

Risk of bias in the six studies incorporating an in vivo component (Pang et al., 2025); Zhang H et al., 2024; Huynh CB et al., 2025; Wang Y et al., 2025; Sun Z et al., 2024; Sun Z et al., 2025) was assessed using SYRCLE's risk of bias tool for animal intervention studies (Hooijmans et al., 2014). The tool comprises ten domains (D1–D10): D1 sequence generation (selection); D2 baseline characteristics (selection); D3 allocation concealment (selection); D4 random housing (performance); D5 blinding of caregivers/investigators (performance); D6 random outcome assessment (detection); D7 blinding of outcome assessor (detection); D8 incomplete outcome data (attrition); D9 selective outcome reporting (reporting); and D10 other sources of bias.

We used an adapted 10-item methodological quality checklist informed by established approaches to assessing the reliability of in-vitro biomedical studies, tailored to the experimental characteristics of MSC-derived paracrine products and UV-induced photoaging models. ToxRTool (Schneider et al., 2009) was considered but was not used as the primary instrument because it was developed principally for assessing the reliability of toxicological studies and does not comprehensively address several study-specific features relevant to this review, including MSC/product characterization and validation of UV-induced photoaging models. Risk of bias was assessed independently by two reviewers, with disagreements resolved by discussion until consensus was reached.

Data Extraction and Synthesis

Data were extracted independently by two reviewers using a standardised extraction form capturing study identification, MSC source and product type (secretome, conditioned medium, extracellular vesicles or engineered cargo), model system and UV induction protocol, delivery route and dose, senescence biomarkers, canonical SASP mediators, matrix

and phenotypic endpoints, and reported mechanistic pathways. Discrepancies were resolved by discussion until consensus was reached. Given substantial heterogeneity in cell and animal models, irradiation spectra and dosing, product characterisation and outcome reporting units, quantitative meta-analysis was not appropriate. Findings were therefore synthesised narratively and organised according to the tier of the senescence–SASP axis at which the intervention acted: upstream oxidative and mitochondrial homeostasis, cell-cycle arrest, secretory output, and matrix and phenotypic outcomes. Endpoint coverage across included studies was tabulated to identify systematic gaps in the evidence base (Table 4).

RESULTS AND DISCUSSION

Study Selection

A systematic search of PubMed ($n = 79$), Scopus ($n = 88$), and Web of Science ($n = 44$) identified a total of 211 records published between 2021 and 2026. After removal of 62 duplicate records, 149 articles were screened by title, of which 127 were excluded for not meeting the predefined eligibility criteria. Twenty-two reports were sought for retrieval, of which seven could not be obtained, leaving 15 full-text articles for eligibility assessment. Following full-text evaluation, seven studies were excluded: five for the absence of senescence-SASP-related outcomes and two for ineligible interventions. Ultimately, eight preclinical studies met the eligibility criteria and were included in the qualitative synthesis. No additional records were identified through websites, organisations, or citation searching. The study selection process is summarised in the PRISMA flow diagram (Figure 1).

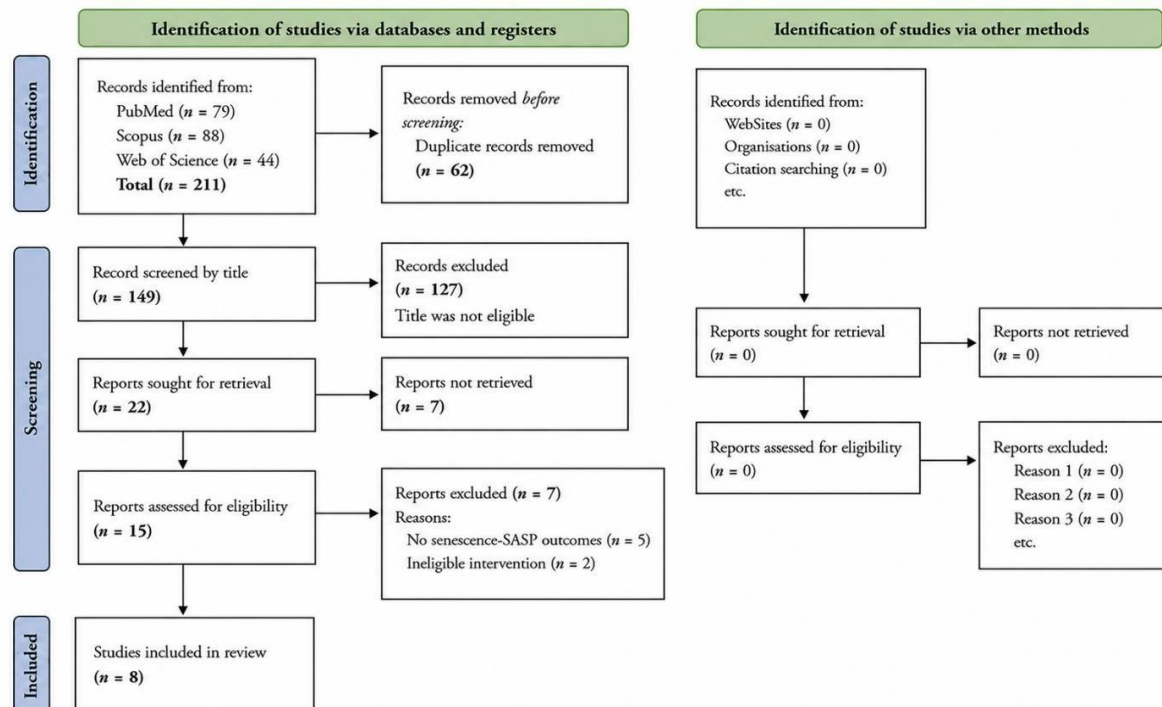


Figure 1. PRISMA flowchart

Study Characteristics

All eight included investigations were preclinical. Six incorporated both in vitro and in vivo components; two (Zou et al., 2022; Zhang et al., 2025) employed exclusively in vitro designs. In vitro models included human dermal fibroblasts (HDF), HaCaT keratinocytes, primary human keratinocytes or reconstructed full-thickness skin equivalents (T-Skin) and were exposed to UVA, UVB or combination UVA/UVB irradiation at doses ranging from 20 mJ/cm² to 1170 mJ/cm² depending on the methodology and cell type. Six studies included an in vivo component using nude mice (Pang et al., 2025; Fu et al., 2024; Wang et al., 2025; Sun et al., 2025), BALB/c mice (Huynh et al., 2025), or immunocompetent ICR mice (Sun Z et al., 2025). UV protocols ranged from fixed-dose alternate-day exposure to minimal erythema dose (MED)-escalating regimens over 4–12 weeks. Another study (Sun Z et al., 2024) also analyzed human tissue comparing PZP expression in specimens of actinic keratosis and squamous cell cancer.

MSC-derived material was obtained from umbilical cord (Sun Z et al., 2024, 2025; Zou X et al., 2022), adipose tissue (Zhang H et al., 2024; Huynh CB et al., 2025; Wang Y et al., 2025; Zhang Y et al., 2025), and hair follicle (Pang et al., 2025) and administered as extracellular vesicles/exosomes, conditioned medium, or engineered cargo-loaded exosomes (miR-125b-5p in Cui H et al., 2025; circ_0011129 in Zhang Y et al., 2025). The delivery route varied between studies and was tested in three studies as a within-study comparison: topical vs subcutaneous injection (Pang et al., 2025); microneedle roller vs intradermal injection (Sun Z et al., 2024); and topical application with occlusion vs untreated control (Huynh CB et al., 2025). Other research utilized direct addition to culture medium (Zou X et al., 2022) or only subcutaneous injection (Zhang H et al., 2024; Wang Y et al., 2025). Outcome measures across the eight studies encompassed senescence markers (SA- β -gal, p16, p21, p53), DNA damage response markers (γ -H2AX, p-ATM, 53BP1), oxidative stress and mitochondrial indices (ROS, mtDNA deletion, PINK1/Parkin pathway components), SASP mediators (IL-6, IL-8/CXCL8, IL-1 β , TNF- α), matrix components (collagen I/III, elastin, MMP-1/2/3), and phenotypic endpoints (wrinkle severity, dermal thickness, transepidermal water loss, hydration). Only one study measured across all six domains (H. Zhang et al., 2024).

Table 1. Comparative summary of preclinical studies of the MSC secretome/EVs/ CM in photoaging and skin senescence (2021–2026).

Study	Source	Model (Inducer)	Delivery Route	Key Molecular Effects	Phenotypic Outcome
Cui H et al., 2025	Hair follicle MSC exosome (miR-125b-5p)	HDF + female nude mice, UVB (in vitro: 20 mJ/cm ² ; in vivo: 150 mJ/cm ² every other day $\times$ 8 wk, followed by 2 wk treatment)	In vitro: 10/20 μ g/mL. In vivo: 20 μ g/100 μ L every other day $\times$ 2 wk; topical vs. S.C. injection	$\downarrow$ SA- β -gal (dose-dependent); $\uparrow$ proliferation and migration; $\downarrow$ ROS; $\uparrow$ Nrf2; $\uparrow$ COL-1/COL-3; $\downarrow$ MMP-1; $\uparrow$ TGF- β 1 and $\uparrow$ p-Smad2/3. Luciferase assay confirmed that miR-125b-5p represses the TGF- β 1 3'UTR, although the increased TGF- β 1 direction remains unresolved. Serum IL-4/IL-6/IL-10 normalized in the S.C. arm. No CDKI	$\downarrow$ WSRS; $\uparrow$ dermal thickness; $\uparrow$ collagen volume fraction in the S.C. injection group only. Topical administration was ineffective. $\uparrow$ CD31.

				(p16/p21/p53) or in vivo senescence marker was measured.	
Zhang H et al., 2024	AD-MSC-EV & UC-MSC-EV (TIMP1)	HaCaT/HKC/HDF/T-Skin + nude mice; UVB (in vitro: 60 mJ/cm ² /day × 3 d; T-Skin: 180 mJ/cm ² /day × 3 d; in vivo: 1→4 MED escalation, ~80 MED total over 8 wk)	In vitro: 200 ng/μL × 24 h. T-Skin: topical to medium × 72 h. In vivo: subcutaneous injection at 10 dorsal sites, 200 μg/mouse, for 4 wk	↓ ROS; ↓ DNA damage; ↓ inflammation; ↓ Notch1 → ↓ p16/p21/p53; ↑ ECM	↑ hydration (↓ TEWL); ↓ wrinkles; ↓ epidermal thickening; ↑ dermal thickness. HUMSC-EV > AMSC-EV in vivo.
Zhang Y et al., 2025	3D-cultured hADSC-derived exosomes loaded with circ_0011129 (3D-circ-Exo)	Human dermal fibroblasts; chronic UVA irradiation (5 J/cm ² /day × 7 d)	Direct in vitro exosome treatment, 50 μg/mL, 24 h pre-treatment	↓ SA-β-gal, p53, p21, p16; ↑ collagen I and elastin; enhanced circ_0011129 delivery	Superior to unmodified exosomes; reduced cellular senescence and ECM degradation/photaging.
Huynh CB et al., 2025	Hypoxia-preconditioned human ADSC exosomes (hypADSC-Exo); 1% O ₂ × 24 h; ultracentrifugation; 102.3 ± 35.4 nm; CD9/CD63/CD81 ⁺ ; TEM cup-shaped, NTA + Bradford	UV-senescent HDF (UVB 1170 + UVA 720 mJ/cm ²) + photoaged BALB/c mice (UVA 51.8 J/cm ² + UVB 5.53 J/cm ² , 12 wk)	In vitro: 10 μg/mL. In vivo: topical 50 and 100 μg/mL, 2×/wk × 6 wk, with occlusion + massage	↓ SA-β-gal; ↓ p16; ↓ p21 (qPCR); ↑ proliferation (Alamar Blue); ↓ cell size; slight ↑ collagen I/III; ↓ MMP-1/-2/-3	↓ wrinkles; ↓ epidermal and dermal thickness; ↑ hydration; ↑ elasticity; ↑ collagen density; comparable to tretinoin without irritation.
Zou X et al., 2022	hUC-MSC-conditioned medium (crude CM)	Serum-starved HaCaT cells + UVB (20 mJ/cm ²)	Direct addition to culture medium	↓ SASP/IL-8, ROS, and p53; modulation of C-FOS/C-JUN, TGF-β, FGF-1, and cyclin A2. CDKN1A (p21) was downregulated after UVB	↓ apoptosis/G1 arrest; ↑ proliferation and motility; recovery of cell morphology.
Wang Y et al., 2025	Human adipose-derived stem cell exosomes (hADSC-Exos)	HDF (UVB 120 mJ/cm ² , 302 nm) + nude mice (n=4/group), UVB 100 mJ/cm ² , 3×/wk × 4 wk	In vitro: 100 μg/mL. In vivo: S.C. injection, 2 doses only (day 0 and day 14)	↑ PINK1/Parkin; ↑ LC3B-II/I; ↓ p62; ↓ TOM20; ↓ ROS; ↓ mtDNA 4,977-bp common deletion; ↓ SA-β-gal; ↓ p21 and p53	↓ epidermal thickening; ↑ collagen density; ↑ HDF motility.
Sun Z et al., 2024	hucMSC-sEVs (104.8 nm)	Neonatal SD rat dermal fibroblasts (xenogeneic)	In vitro: 1×10 ¹⁰ /mL, 24 h pre-treatment. In	↑ PZP → ↓ MMP-1 (direct binding, CoIP + colocalization); ↑ COL1A1; ↑ SIRT3; ↓ ROS; ↓ SA-β-	↓ desquamation/wrinkling; ↑ collagen volume

		pairing), UVA 5 J/cm ² × 5; BALB/c nude mice (n=6/group), UVA+UVB, 1 MED escalating, 7 or 10 rounds	vivo: microneedle roller, 5×10 ¹⁰ particles; superior to intradermal injection based on imaging + IF distribution	gal; ↓ p-ATM/γ-H2AX/53BP1. PZP OE/si rescue. Comparators: 0.05% retinoic acid (positive control) and NMN ± sEVs	fraction; preserved dermal thickness; outperformed retinoic acid.
Sun Z et al., 2025	Human umbilical cord MSC-derived small extracellular vesicles (hucMSC-sEVs)	Rat dermal fibroblasts (UVA 365 nm / UVB 311 nm) + ICR immunocompetent mice, UVA+UVB, 1 MED + 0.5 MED/cycle × 4 cycles	In vitro: 1×10 ¹⁰ particles/mL . In vivo: microneedle roller	GATA2 → binds PZP promoter (ChIP + dual-luciferase) → ↑ PZP → ↓ GRP75 → ↓ mitochondrial Ca ²⁺ overload and ↓ mtROS; ↓ SA-β-gal, ↓ p53, ↓ γ-H2AX; ↑ COL1A1; ↓ IL-6 mRNA. si-GATA2/oe-GATA2 sEVs + MKT-077 (GRP75 inhibitor) phenocopied the effects	↓ wrinkles; ↓ stratum corneum thickening; ↑ collagen density.

Risk of Bias Assessment Results

Risk of bias across the six in vivo studies was predominantly unclear rather than demonstrably low, driven by under-reporting rather than by documented methodological failure. All six declared randomised allocation, but only one: (Wang Y et al, 2025) specified the sequence-generation method or described any concealment procedure. No study reported randomised housing, blinding of animal caregivers, randomised outcome assessment, or blinded outcome assessment; all four of these domains were therefore rated unclear in every study. Selective outcome reporting was judged low risk throughout, as all outcomes pre-specified in the Methods were reported. The principal identifiable high-risk domains were baseline comparability, where (Huynh CB et al, 2025) compared UV-exposed 6-8-week-old mice against an 18-20-week-old control cohort, and incomplete outcome data, where three studies (Sun Z et al, 2024; Huynh CB et al, 2025; (Pang et al., 2025) analysed substantially fewer animals than were allocated without explanation, or did not fix group size a priori. (Wang Y et al, 2025) was the only study to satisfy the selection-bias domains and to state explicitly that no animals or experimental units were excluded. The result of the risk of bias assessment in the table below, with the description : L = low risk; H = high risk; U = unclear risk (insufficient reporting to permit judgement). (Sun Z et al, 2024) employed neonatal rat dermal fibroblasts (in vitro) in conjunction with BALB/c nude mice (in vivo), introducing species incongruence in pathway translation that limits cross-compartment mechanistic inference. (Huynh CB et al, 2025) compared UV-exposed 6-8 week-old mice against an 18-20-week-old control cohort, with the ten-week age differential introducing baseline physiological variation independent of UV exposure. (Pang et al., 2025) did not measure senescence markers in the in vivo photoaging model, restricting senescence assessment to in vitro fibroblasts and inferring in vivo senescence suppression from serum cytokine normalisation alone.

Table 2. SYRCLE Risk of Bias Assessment Results across six In-vivo Studies

Study (year)	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10
Sun Z, 2024	U	L	U	U	U	U	U	H	L	H
Sun Z, 2025	U	U	U	U	U	U	U	U	L	L
Huynh CB, 2025	U	H	U	U	U	U	U	H	L	H
Wang Y, 2025	L	L	L	U	U	U	U	L	L	L
Zhang H, 2024	U	U	U	U	U	U	U	U	L	U
Cui H, 2025	U	L	U	U	U	U	U	H	L	H

The methodological quality of the in-vitro experiments was evaluated using a predefined 10-item checklist. Each item was scored as 1 (adequately addressed), 0.5 (partially addressed) or 0 (not addressed). The study comprised selection of the cell model, characterization of the UV model, treatment concentration, control design, reference comparators, breadth of senescence markers, mechanistic investigation, characterization of the MSC-derived product, biological replication and statistical technique. Higher scores denoted more complete reporting and design. (Zou X et al, 2022) received a score of 6.5/10, suggesting that cell selection, UV exposure, controls, mechanistic analyzes, replication and statistical methods were adequately reported, but dose-response assessment, reference controls, breadth of senescence markers and MSC-derived product characterization were not. (Zhang Y et al, 2025) 7.0/10 with its strengths being in cell/model characterisation, control design, senescence-marker evaluation, replication, statistical reporting, but with certain limitations, such as limited concentration testing, weak mechanistic characterization, and insufficient EV characterization.

Table 3. Bespoke quality checklist for in vitro-only included studies

#	Item	Zou X et al, 2022	Zhang Y et al, 2025
1	Cell source/line stated and appropriate to model	1 = HaCaT (Procell) and hUC-MSC (Procell), commercial characterized lines, mycoplasma-tested	1 = primary HDF (paediatric foreskin, ethics-approved) and primary hADSC (liposuction donors, ethics-approved), confirmed by flow cytometry (CD90+/CD105+/CD34-/CD45-) and tri-lineage differentiation
2	UV dosimetry fully reported (wavelength, device, intensity, dose)	1 = SH2B-type UVB lamp, 500 μ W/cm ² , 40 s at 20 cm, 20 mJ/cm ²	1 = 365 nm UVA, 2.78 mW/cm ² , 5 J/cm ² /day x 7 days
3	Concentration range tested (dose-response design)	0 = single CM volume (matched to CGM), no titration	0 = single 50 μ g/mL dose, no titration
4	Negative/vehicle control included	1 =Ctrl group (UVB- , CGM)	1 = light-shielded NC group
5	Positive or reference comparator included	0 = no comparator beyond Ctrl/UVB	0.5 = 3D-Exo serves as internal comparator to 3D-circ-Exo; no external reference agent (e.g. retinoic acid)
6	Multiple senescence markers assessed	0.5 = p53, p21 (CDKN1A) only; no SA- β -gal, no p16	1 = SA- β -gal, p53, p21, p16 all reported 0.5 = circRNA cargo validated
7	Mechanistic/molecular	1 = paired transcriptomic + proteomic profiling,	(divergent/convergent PCR, Sanger sequencing, RNase R resistance);

	readout beyond phenotype	GO/KEGG enrichment, qRT-PCR and Western blot validation	proposed miR-6732-5p sponging mechanism cited from prior work, not re-tested in this paper
8	EV/CM characterisation reported (source validation)	0 = crude conditioned medium; no particle/protein characterisation performed or reported	0 = standard differential ultracentrifugation protocol described, but no NTA, TEM, or tetraspanin marker (CD9/CD63/CD81) data reported anywhere in the paper
9	Replicate number (n) per condition stated	1 = (n = 3) biological replicates stated throughout (proliferation, apoptosis, cell cycle, qPCR in triplicate)	1 = (n = 3) biological replicates stated explicitly
10	Statistical method specified	1 = SPSS v20; paired/unpaired Student's t-test with Welch's correction based on F-test for variance	1 = Levene's test for variance homogeneity, Welch-corrected t-tests, ANOVA with Fisher's LSD or Dunnett's T3 post hoc, Bonferroni-adjusted p-values, effect sizes (η^2 , Cohen's d) reported
	Score	6.5 / 10	7 / 10
	Qualitative rating	Moderate methodological quality	Moderate-high methodological quality

Table 4. Endpoint coverage matrix across the eight included studies

Study	SA- β -gal	p16	p21	p53	γ H2A X /DDR	Lamin B1	IL-6	IL-8/CXCL8	IL-1 β	TNF- α	MMPs	Collagen I/III	Elastin	Group (n)
Cui H., 2025	✓	-	-	-	-	-	✓	-	-	-	✓ (MMP 1 only)	✓	-	≥5/group
Zhang H., 2024	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	5–6/group
Zhang Y., 2025	✓	✓	✓	✓	-	-	-	-	-	-	-	✓	✓	N/A
Huynh CB., 2025	✓	✓	✓	-	-	-	-	-	-	-	✓	✓	-	10/group
Zou X., 2022	-	-	transcriptomic	✓	-	✓	✓	✓	- (IL-1 α)	✓	✓	-	-	N/A
Wang Y., 2025	✓	-	✓	✓	-	-	-	-	-	-	-	✓	-	4/group
Sun Z., 2024	✓	✓	✓	✓	✓	-	-	-	-	-	✓ (MMP 1 only)	✓ (COL1 A1 only)	-	6/group
Sun Z., 2025	✓	-	-	✓	✓	-	✓	-	-	-	-	✓ (COL1 A1 only)	-	6/group
Total (8)	7	4	5	6	3	2	4	2	1	2	5	7	2	-

Photoaging can be understood as a linear cascade in which an initial photochemical injury is progressively converted into a self-sustaining tissue pathology (Figure 2). Ultraviolet radiation damages nuclear and mitochondrial DNA both directly and through the generation of reactive oxygen species (ROS), with UVB acting predominantly on the epidermis and UVA penetrating to the dermal fibroblast compartment (Fitsiou et al., 2021; (Franco et al., 2022). Mitochondrial DNA is particularly vulnerable, lying adjacent to the electron transport chain and possessing limited repair capacity; the resulting respiratory impairment generates further ROS, establishing a self-amplifying loop now regarded as a central driver of ageing rather than a consequence of it (Miwa et al., 2022).

Persistent DNA damage activates the DNA damage response, with ATM phosphorylation, γ -H2AX foci formation and p53 stabilisation. Where damage exceeds repair capacity, the transient cell-cycle pause becomes permanent: p53 induces p21^{CIP1}, p16^{INK4a} is engaged independently, and the cell enters senescence, viable and metabolically active but irreversibly arrested, with morphological enlargement, elevated senescence-associated β -galactosidase activity and loss of Lamin B1 (Huang W et al, 2022). Current consensus holds that no single marker defines this state and that senescence must be identified by a combination of features (Gorgoulis et al., 2019).

The pathological weight of the axis lies in what follows. Senescent cells initiate the senescence-associated secretory phenotype (SASP), secreting interleukin-1 β , IL-6, IL-8, TNF- α and matrix metalloproteinases (MMPs) (Fitsiou E et al, 2021; (Cuollo et al., 2020). This converts an arrested cell into an active source of tissue injury through two routes. First, secreted MMPs degrade collagen and elastin faster than the remaining functional fibroblasts can replace them. Second, SASP cytokines induce senescence in neighbouring healthy cells, paracrine or bystander senescence, allowing a limited number of primary senescent cells to seed a substantially larger population (Admasu et al., 2021). The cumulative effect of chronic matrix catabolism is the clinical and histological phenotype of photoaged skin: wrinkling, laxity, xerosis and disorganised, fragmented dermal collagen (Franco AC et al, 2022).

This cascade identifies three distinct points of intervention: upstream protection of mitochondrial and redox homeostasis; interruption of entry into arrest; and suppression of secretory output from cells already arrested. Agents acting through the third mechanism are termed senomorphics, and are conceptually distinct from senolytics, which eliminate senescent cells (Takaya et al., 2023). The mesenchymal stem cell (MSC) secretome is of interest in this context because extracellular vesicles (EVs) deliver proteins, microRNAs, circular RNAs and lipids simultaneously, and may therefore engage several tiers of the cascade concurrently (Kumar MA et al,2024; (Hajialiasgary Najafabadi et al., 2024). This review examined the extent to which that expectation is supported by the available preclinical evidence.

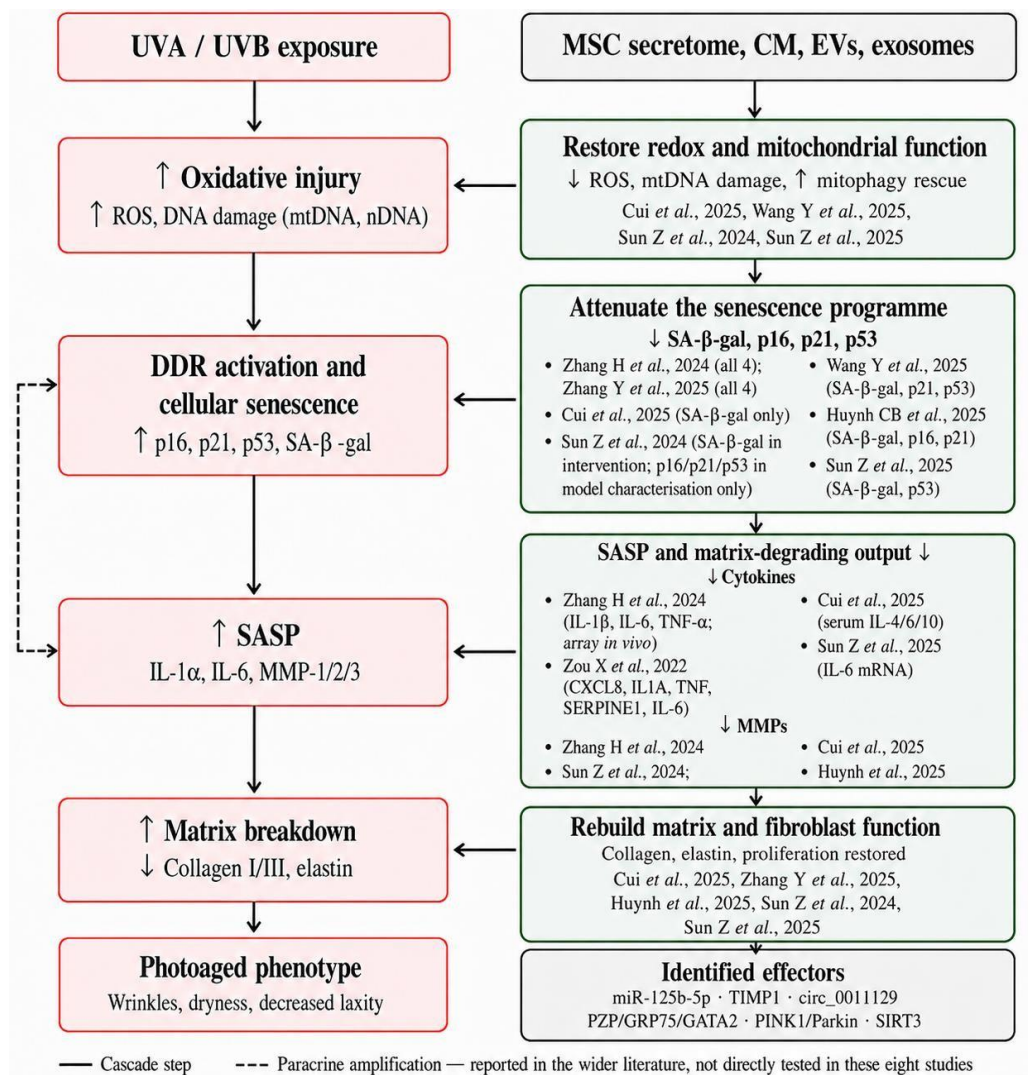


Figure 2. The Senescence-SASP Axis and Sites of Action of MSC Secretome/CM/EVs/exosomes

Evidence for intervention at the upstream tier

Four included studies addressed this tier, two establishing causality and two providing supporting observations. Together they position mitochondrial quality control as a mediator of secretome activity rather than a correlate. (Wang Y *et al.*, 2025) demonstrated that adipose MSC-derived exosomes restore PINK1/Parkin-mediated mitophagy in UVB-exposed human dermal fibroblasts, raising PINK1, Parkin and the LC3B-II/I ratio while lowering p62 and TOM20, with a corresponding reduction in the 4,977-base-pair mitochondrial common deletion, an established index of accumulated mitochondrial damage. Silencing PINK1 by siRNA abolished the reduction in ROS, mtDNA deletion, SA-β-gal positivity, p21 and p53, establishing that the anti-senescence effect is mitophagy-dependent.

(Sun *et al.*, 2025) identified an independent route to the same organelle. Human umbilical cord MSC-derived small EVs (hucMSC-sEVs) were shown to carry the transcription factor GATA2, which binds the promoter of pregnancy zone protein (PZP), confirmed by chromatin immunoprecipitation and dual-luciferase reporter assay. Elevated PZP restrained GRP75 at endoplasmic reticulum-mitochondria contact sites, relieving

mitochondrial calcium overload, restoring membrane potential and reducing mitochondrial ROS. The pathway was tested bidirectionally: sEVs from GATA2-knockdown MSCs lost efficacy, sEVs from GATA2-overexpressing MSCs gained it, and the selective GRP75 inhibitor MKT-077 reproduced the effect independently. Notably, this mechanism was prospectively predicted: (Sun et al., 2024) concluded by proposing that hucMSC-sEVs must carry an unidentified transcription factor acting on the PZP promoter, and specified dual-luciferase validation as the intended next step. The PZP axis is therefore the only mechanism in this evidence base to have been hypothesised in one publication and confirmed in a subsequent one.

Supporting observations at this tier were reported by (Sun Z et al, 2024), in which sEV pretreatment restored SIRT3 and reduced the full DNA damage response panel (p-ATM, γ -H2AX, 53BP1), and by (Pang et al., 2025), in which Nrf2 was upregulated alongside reduced ROS. Across four studies employing three MSC sources, the common endpoint was restoration of endogenous mitochondrial and antioxidant homeostasis rather than exogenous radical scavenging. Independence at this tier is partial: (Sun Z et al, 2024) and (Sun Z et al, 2025) originate from the same research group and the same hucMSC-sEV source, with the GATA2/PZP/GRP75 pathway characterised in the second study explicitly extending a mechanism proposed in the first. The upstream tier is therefore better described as two independent groups (Wang Y et al., 2025, via PINK1/Parkin; Sun Z et al., 2024/2025, via GATA2/PZP/GRP75) rather than four independent lines of evidence.

Evidence for intervention at the arrest tier

All eight investigations measured at least one senescence marker. They varied primarily in the thoroughness of route evidence. The most extensively characterized mechanism revealed in the review was by (Zhang H et al, 2024). TIMP1 was identified as the major common cargo of adipose- and umbilical cord-derived EVs by proteomic screening. TIMP1 was discovered to inhibit ADAM10, therefore blocking Notch1 S2 cleavage, reducing the Notch intracellular domain and its downstream effector HES1 and subsequently decreasing p16, p21 and p53 (Zhou et al., 2022). The route was pharmacologically bracketed in both directions, with the Notch activator valproic acid abrogating EV efficacy and the ADAM10 inhibitor GI254023X recapitulating EV efficacy in the absence of EVs. Recombinant TIMP1 at 5 ng/mL did reduce ROS, γ -H2Ax and SA- β -gal, and siRNA reduction of TIMP1 promoted senescence markers. These findings were duplicated over four model tiers, HaCaT keratinocytes, primary human keratinocytes, dermal fibroblasts and a reconstructed full thickness human skin equivalent. The most clear graded effect at this tier was presented by (Zhang Y et al, 2025). SA- β -gal positivity was increased from 5% to 70% after 7 days of UVA exposure, decreased to 50% with unmodified three-dimensionally cultivated exosomes and to 20% with circ_0011129-loaded exosomes, with concomitant decreases in p53, p21 and p16 and recovery of collagen I and elastin. The internal comparison shows that modified cargo can increase the baseline secretome activity.

(Huynh CB et al, 2025) reported decreased SA- β -gal, p16 and p21 with improved proliferation, and interpreted the accompanying decrease in mean cell size as expansion of the non-senescent population rather than reversal of established senescence - a distinction consistent with the senomorphic classification adopted here.

(Sun Z et al, 2024) turned PZP into a verified mediator by direct manipulation in fibroblasts, moving it from an associated marker: overexpression reduced SA- β -gal in the absence of vesicle treatment and knockdown attenuated the effect of sEVs on senescence, MMP-1 suppression, SIRT3 restoration and DNA damage markers.

(Pang et al., 2025) demonstrated a dose-dependent decrease in SA- β -gal in UVB-exposed fibroblasts, the clearest dose–response for senescence in the review. However, SA- β -gal was the only senescence marker examined. No cyclin-dependent kinase inhibitor was measured in either compartment.

A design feature shared across most of the included studies bears on the senopreventive classification adopted in this review. In vitro, secretome or EV treatment was administered either before UV exposure (Sun Z et al., 2024, Sun Z et al, 2025; Zhang Y et al., 2025) or within 24 hours of a single exposure, prior to the establishment of a senescent phenotype (Zou X et al., 2022). In vivo, treatment was most commonly co-administered alongside an ongoing UV induction protocol rather than introduced after photoaging was established (Zhang H et al., 2024; Wang Y et al., 2025; Sun Z et al., 2024, Sun Z et al, 2025). Only two studies administered treatment after a completed induction period, once the photoaged phenotype was present (Pang et al., 2025), subcutaneous arm; Huynh CB et al., 2025). This design pattern, intervention before or during senescence induction rather than after it is established, is a stronger basis for the senomorphic/senopreventive classification used throughout this review than the molecular data alone, and it correspondingly limits what the evidence base can say about reversal of already-established senescent phenotypes.

Evidence for intervention at the secretory tier

Assessment of the SASP was substantially less complete than assessment of arrest. (Zhang H et al, 2024) were the only investigators to characterise a canonical SASP panel alongside arrest markers within a single experimental system, in vitro and in vivo. IL-1 β , IL-6 and TNF- α were quantified by qRT-PCR and ELISA in keratinocytes, fibroblasts and the T-Skin model, and an inflammation antibody array applied to murine dorsal skin demonstrated UV-induced elevation of GCSF, IFN- γ , IL-6 and GM-CSF among others, each restrained by EV treatment. The matrix-degrading arm was captured in parallel, with reductions in MMP1, MMP3 and MMP9, restoration of TIMP1, and recovery of Lamin B1.

(Zou X et al, 2022) applied paired transcriptomic and proteomic profiling to hUC-MSC conditioned medium in serum-starved HaCaT keratinocytes, generating an unbiased rather than targeted characterisation. The UVB transcriptome carried a recognisable SASP signature (CXCL8, IL-6, IL1A, MMP-9, TNF and SERPINE1 upregulated; LMNB1 downregulated), and conditioned medium reversed CXCL8, MYC, FGF-1 and EREG. Interpretation is constrained by the model: a single 20 mJ/cm² UVB exposure assayed at 24 hours, without SA- β -gal or p16 assessment, and with CDKN1A (p21) downregulated (log₂FC –1.04), a pattern more consistent with acute DNA damage response and apoptosis than with an established senescence programme. This study is therefore best regarded as evidence for suppression of an inflammatory-secretory phenotype rather than of senescence as such. (Pang et al., 2025) measured serum IL-4, IL-6 and IL-10 in photoaged mice, each normalised by subcutaneous exosome administration. Because senescence was assessed in cultured cells while cytokines were measured in blood, the two tiers of the axis were not linked within a single compartment. Sun Z et al. (2025) measured a single canonical mediator, IL-6 at the

transcript level, alongside SA- β -gal and p53 in the same fibroblast and murine systems; this links the two arms of the axis within one compartment but does not constitute characterisation of the secretory phenotype. The remaining four studies (Zhang Y et al., 2025; Huynh CB et al., 2025; Wang Y et al., 2025; Sun Z et al., 2024) measured senescence markers without any SASP mediator.

Evidence at the matrix and phenotypic tier

Two independent groups converged on delivery or induction of endogenous protease inhibitors as the proximate mechanism of collagen preservation. (Zhang H et al, 2024) identified TIMP1, a physiological inhibitor of MMPs and ADAMs, while Sun Z et al. (2024) identified PZP, an α 2-macroglobulin family endopeptidase inhibitor, and confirmed direct PZP-MMP-1 binding by co-immunoprecipitation and immunofluorescence colocalisation in both fibroblasts and skin tissue. This mechanism acts at the enzymatic rather than the transcriptional layer and is therefore independent of the synthetic capacity of the residual fibroblast population.

Transcriptional routes to matrix preservation were reported by (Pang et al., 2025), who demonstrated upregulation of collagen I and III and downregulation of MMP-1 via TGF- β 1/Smad2/3 signalling, and by (Huynh CB et al, 2025), who observed the same directional pattern for collagen I/III and MMP-1, MMP-2 and MMP-3, without reaching statistical significance. Elastin, the principal component of the elastotic lesion characteristic of human photoaged skin, was assessed in only two studies, by Western blot (Zhang Y et al, 2025) and Verhoeff-Van Gieson staining (Zhang H et al, 2024).

At the phenotypic level, several studies incorporated clinically established comparators. (Sun Z et al, 2024) benchmarked hucMSC-sEVs against 0.05% retinoic acid and reported superior preservation of collagen volume fraction and dermal architecture. (Huynh CB et al, 2025) benchmarked topical hypoxia-preconditioned exosomes against 0.05% tretinoin, achieving comparable wrinkle reduction while the tretinoin arm developed erythema and scaling. (Pang et al., 2025) applied the validated Wrinkle Severity Rating Scale, and (Zhang H et al, 2024) additionally quantified transepidermal water loss as a measure of barrier function.

Delivery route

Four investigations focused on cutaneous delivery. The results were consistent. In Cui H et al. (2025), both topical and subcutaneous delivery were used as parallel arms in the same animals, with subcutaneous injection improving wrinkle score, skin thickness and collagen volume fraction, and topical treatment having no discernible impact. (Sun Z et al, 2024) compared microneedle roller against intradermal injection using in vivo fluorescence imaging and histological distribution analysis, demonstrating a stronger and more uniform dermal signal with microneedle delivery, which was adopted for subsequent work by the same group (Sun Z et al., 2025). (Huynh CB et al, 2025) obtained effectiveness by topical method but under 1 h of occlusive dressing with 2 min of massage, with penetration in part owing to the murine stratum corneum thickness of $\sim$ 5 μ m.

To summarize, the evidence suggests that an intact stratum corneum acts as a functional barrier to EV transport and thus unassisted topical treatment should not be presumed to reach the dermal fibroblast compartment in human skin. Microneedle-assisted

administration is the most favorable approach identified within this data base (Lyu et al., 2023).

Limitations of the evidence base

Only (Zhang H et al, 2024) characterised a canonical SASP panel alongside arrest markers within a single system, with (Sun Z et al, 2025) reporting a single mediator (IL-6 mRNA) in the same compartment; as the SASP constitutes the mechanism by which senescent cells damage surrounding tissue, current claims of senotherapeutic activity therefore rest predominantly on the arrest arm of the axis. Bystander senescence was not examined in any included study, despite its proposed role in the accumulation of senescent cells (Admasu TD et al, 2021). The required experiment, transfer of conditioned medium from treated or untreated UV-senescent fibroblasts onto naive recipients, with quantification of secondary senescence, has not been performed. Preconditioning effects remain untested: (Zhang Y et al, 2025) compared three-dimensionally cultured exosomes against cargo-loaded exosomes of the same origin rather than against two-dimensionally cultured preparations, and (Huynh CB et al, 2025) included no normoxic comparator; neither study contains the arm required to support a preconditioning claim.

Dose-response synthesis is precluded by non-comparable units, with five studies reporting protein mass, two reporting particle number and one reporting conditioned medium volume. MISEV2023 recommends dual reporting of particle count and protein content (Welsh et al., 2024). Phenotypic endpoints are not uniformly interpretable. Dermal thickness decreased following UV exposure in the nude-mouse models of (Pang et al., 2025; Zhang H et al, 2024; Sun Z et al, 2024), but increased in the haired BALB/c model of (Huynh CB et al, 2025), consistent with elastotic thickening described in human photoaged skin; this endpoint should not be pooled across strains. Spectral heterogeneity is a further constraint, with UVA-only, UVB-dominant and combined UVA/UVB protocols represented. The evidence base also has limited group-level independence: two of the eight included studies (Sun Z et al., 2024; Sun Z et al., 2025) derive from the same laboratory and the same hucMSC-sEV source, with the second study's mechanism prospectively predicted by the first. This does not weaken the individual findings, which were internally validated by bidirectional manipulation (knockdown/overexpression) in each case, but it means the upstream and PZP-related conclusions rest on independent confirmation from only one external group rather than two.

Immunodeficient models predominate, with four of six *in vivo* studies using nude mice, in which immune surveillance of senescent cells is absent by construction. (Sun Z et al, 2025) addressed this by adopting immunocompetent ICR mice. No included study is an interventional clinical trial; human tissue was examined only observationally, in the actinic keratosis and squamous cell carcinoma series reported by (Sun Z et al, 2024). No study included a post-treatment observation period or extended follow-up beyond twelve weeks, precluding assessment of durability of effect or delayed dysplastic change. Also, one detail that remains to be resolved comes from (Pang et al., 2025), where luciferase reporter assays confirmed repression of the TGF- β 1 3'UTR by miR-125b-5p. However, exogenous miR-125b-5p mimic treatment in the same study increased TGF- β 1 protein expression rather than decreased it, leaving the direction of this regulatory arm unresolved. This does not detract from the main senescence findings of the study, as these were evaluated independently of the

TGF- β 1 axis. However, the miR-125b-5p/TGF- β 1/Smad mechanism presented as the mechanism in the title of the paper is not totally internally consistent as reported.

Long-term safety was not assessed. All included studies report suppression of p16, p21 and/or p53 in chronically UV-exposed skin, the checkpoints that constrain actinic carcinogenesis, without corresponding tumour-watch endpoints. Within their human tissue series, (Sun Z et al, 2024) observed reduced PZP in actinic keratosis and squamous cell carcinoma in situ with a rebound in invasive squamous cell carcinoma, an observation the authors identified as requiring further clinical data.

CONCLUSION

The strongest evidence was observed at the upstream and cell-cycle arrest levels of the senescence–SASP axis. Restoration of mitochondrial quality control was mechanistically demonstrated through PINK1-dependent mitophagy and the GATA2/PZP/GRP75 signaling axis, a mechanism initially proposed by the same research group and subsequently supported by later findings. The TIMP1–ADAM10–Notch1–HES1–p16/p21/p53 signaling pathway was investigated using pharmacological interventions, target knockdown, and recombinant protein rescue experiments across four experimental model systems, including reconstructed human skin. Preservation of the dermal extracellular matrix (ECM) was consistently observed, partly through the delivery or induction of endogenous protease inhibitors. Improvements in photoaging-related phenotypes were also demonstrated in comparisons with retinoic acid and tretinoin. However, two major limitations constrained the interpretation of these findings. First, the secretory component of the senescence–SASP axis was evaluated in only four studies. A comprehensive panel of SASP mediators was assessed alongside cell-cycle arrest markers within the same experimental system in only one study, whereas another examined only a single mediator. Consequently, evidence supporting senotherapeutic activity relied predominantly on changes in cell-cycle arrest markers rather than direct assessment of the secretory phenotype responsible for senescence-associated tissue damage. Furthermore, none of the included studies investigated the paracrine transmission of senescence. Second, the intact stratum corneum consistently restricted extracellular vesicle (EV) penetration, suggesting that conventional topical administration without penetration-enhancing techniques may be insufficient to deliver EVs to dermal fibroblasts in human skin. Microneedle-assisted delivery emerged as the most promising administration approach among those investigated. Overall, the observed effects were more appropriately characterized as senomorphic and predominantly senopreventive rather than senolytic. Most studies administered mesenchymal stem cell (MSC)-derived paracrine products before or during ultraviolet (UV) exposure rather than after cellular senescence had been established, and none demonstrated the selective elimination of preexisting senescent cells. Moreover, no interventional clinical trials were identified, and long-term safety remained unestablished, particularly regarding the sustained downregulation of p16^{INK4a}, p21^{CIP1}, and p53 signaling in chronically UV-exposed skin.

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